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Health Effects Assessment for Methyl Ethyl Ketone

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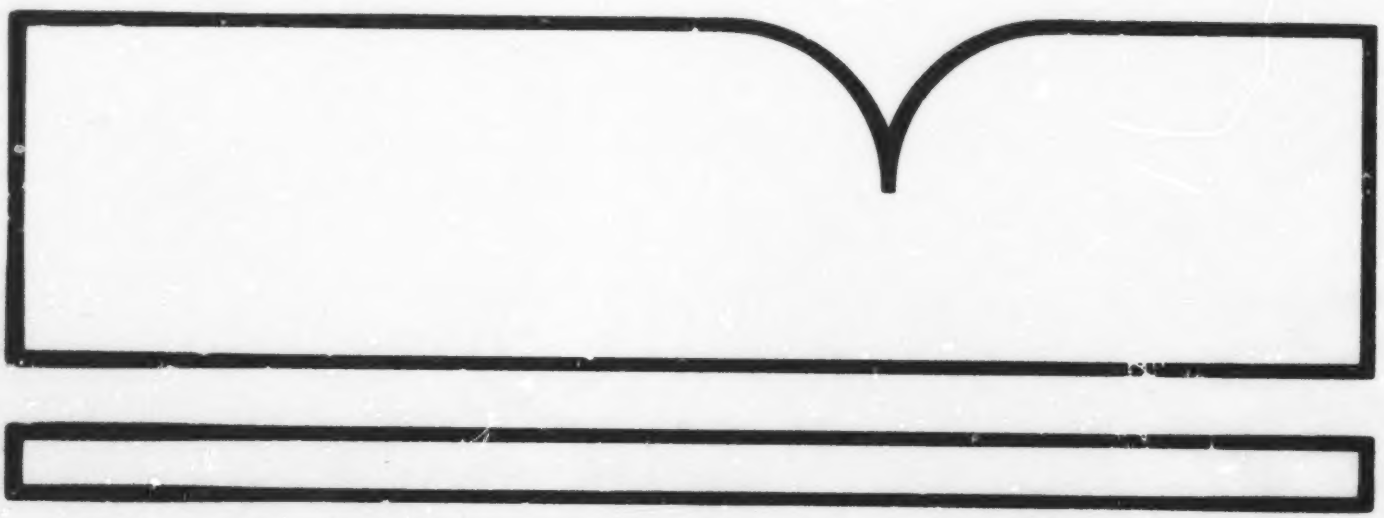

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HEALTH EFFECTS ASSESSMENT FOR METHYL ETHYL KETONE

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a ...mi-nary interim assessment of adverse health effects associated wi... ...ethyl ethyl ketone. All estimates of acceptable intakes and carcinogeni... potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1985. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1983. Reportable Quantity Document for 2-Butanone (Methyl Ethyl Ketone). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Methyl Ethyl Ketone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

A number of subchronic inhalation studies using experimental animals are available, which suggest threshold exposure levels for liver damage, neurological impairment and fetotoxicity. An RfD_O of 3.0 mg/day was based on a NOAEL of 235 ppm from a subchronic inhalation study and was verified by the U.S. EPA (1985b). No chronic exposure data and no oral data were available; however, an RfD_{SO} of 32 mg/day, an RfD_{SI} of 64 mg/day and an RfD_I of 6 mg/day were estimated based on the subchronic inhalation data. These estimates should be reviewed when adequate chronic data become available. A CS of 9.6 was calculated for methyl ethyl ketone based on decreased body weight gain in rats exposed by inhalation.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
K_{oc}	Soil sorption coefficient
K_{ow}	Log octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RFD_S	Subchronic reference dose
RFD_{SI}	Subchronic inhalation reference dose
RFD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of methyl ethyl ketone (CAS No. 78-93-3) are summarized below.

Chemical class:	aliphatic ketone	
Molecular weight:	72.1	Verschueren, 1983
Vapor pressure at 20°C:	77.5 mm Hg	Verschueren, 1983
Water solubility at 20°C:	268 g/ℓ	Papa and Sherman, 1981
Log K_{ow}:	0.29	Hansch and Leo, 1985
K_{oc}:	4.5-50 (estimated)	U.S. EPA, 1985a
Bioconcentration factor	0.5-1 (estimated)	U.S. EPA, 1985a
Half-life in air:	14-15 hours	Graedel, 1978; U.S. EPA, 1985a
in water:	few days	U.S. EPA, 1985a

The primary removal mechanism for atmospheric methyl ethyl ketone will be direct photolysis (U.S. EPA, 1985a). Detection of methyl ethyl ketone in rain, cloudwater and airborne particulate matter suggests that small amounts of this compound may also be removed from the atmosphere by wet and dry deposition (U.S. EPA, 1985a).

In water, methyl ethyl ketone is expected to be removed by evaporation (half-life of 3-12 days) and biodegradation (half-life >3 days) (NLM, 1987). Direct photolysis near water surfaces may also be possible (U.S. EPA, 1985a). Bioconcentration in aquatic organisms and adsorption to sediments are not expected to be important fate processes (U.S. EPA, 1985a).

The half-life of methyl ethyl ketone in soil could not be located in the literature searched. By analogy to aquatic media, the dominant fate processes in soil are expected to be volatilization and biodegradation (NLM, 1987; U.S. EPA, 1985a). Methyl ethyl ketone residue may be susceptible to significant leaching (NLM, 1987; U.S. EPA, 1985a). It has been speculated that the half-life of methyl ethyl ketone in soil would be on the order of a few days.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative data on the oral absorption of methyl ethyl ketone are not available, but absorption from the gastrointestinal (GI) tract can be inferred from systemic toxic effects observed after acute oral administration (Lande et al., 1976). In male rats, the peak blood level of methyl ethyl ketone (0.95 mg/mℓ) was reached within 4 hours following oral administration of a 1690 mg/kg dose of the compound in water, indicating rapid absorption from the GI tract (Dietz et al., 1981; Dietz and Traiger, 1979).

2.2. INHALATION

Perbellini et al. (1984) reported a mean blood concentration of methyl ethyl ketone of 2630±2450 µg/ℓ (range: 842-9573 µg/ℓ) in workers exposed to methyl ethyl ketone and several other compounds and that 70% of the inhaled methyl ethyl ketone was retained in the alveolar space. The environmental concentration correlated significantly with the alveolar concentration of methyl ethyl ketone, which in turn correlated significantly with blood levels. At the end of an 8-hour work shift, the urine of workers exposed to a mean concentration of methyl ethyl ketone in the air of 101±67 µg/ℓ contained a mean concentration of 487±277 µg/ℓ (Perbellini et al., 1984). Miyasaka et al. (1982) reported that the urinary levels of methyl ethyl ketone rose rapidly during the first 2 hours of an 8-hour work shift in occupationally exposed workers and the levels correlated with the measured levels in the air. Therefore, pulmonary absorption of methyl ethyl ketone appears to occur rapidly during occupational exposure.

3. TOXICITY IN H'MANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the effects of oral exposure to methyl ethyl ketone on humans or experimental animals were not located in the available literature.

3.1.2. Inhalation. The subchronic inhalation studies on methyl ethyl ketone are summarized in Table 3-1. Cavender et al. (1983) exposed both sexes of Fischer 344 rats to methyl ethyl ketone at concentrations of 0, 1250, 2500 or 5000 ppm (0, 3687, 7373 or 14,746 mg/m^3), 6 hours/day, 5 days/week for 90 days. There were no treatment-related effects at the 1250 ppm level; SGPT activity in female rats was elevated at the 2500 ppm level. At the 5000 ppm level, effects were more severe: these included depressed mean body weight; slight but significant increases in liver weight, liver-to-body weight ratio, and liver-to-brain weight ratio; significantly decreased SGPT activity; and increased alkaline phosphatase, potassium and glucose values in treated females.

Exposure of Wistar rats to methyl ethyl ketone at a level of 0 or 200 ppm (0 or 590 mg/m^3), 12 hours/day, 7 days/week for 24 weeks reportedly resulted in slight neurological effects of unknown biologic significance measurable only at 4 months of treatment (Takeuchi et al., 1983), but in another study using rats exposed to 1125 ppm (3318 mg/m^3) continuously for 5 months did not result in neuropathy, as indicated by absence of paralysis (Saida et al., 1976). In both studies, only a single toxicological endpoint was examined, such as motor nerve conduction velocity, mixed nerve conduction velocities, or distal motor latency (Takeuchi et al., 1983) or paralysis (Saida et al., 1976).

TABLE 3-1

Subchronic Inhalation Toxicity Testing of Methyl Ethyl Ketone*

Species/Strain	Sex	Number at Start	Exposure	Effects	Reference
Rats/F344	M/F	15/sex/ exposure level	0, 1250, 2500 or 5000 ppm, (0, 3687, 7373 or 14,746 mg/m³), 6 hours/day, 5 days/week, for 90 days	No neuropathologic or histopathologic changes and no effect on clinical parameters or growth at the 1250 ppm level. At the 2500 ppm level, female rats had elevated SGPT activity. At the 5000 ppm level, treatment-related effects included depressed mean body weight; slight but significant increases in liver weight, liver-to-body weight ratio, and liver-to-brain weight ratio; significantly decreased SGPT activity; and increased alkaline phosphatase, potassium and glucose values in treated females.	Cavender et al., 1983
Rats/Wistar	M	8/exposure level	0 or 200 ppm (0 or 590 mg/m³), 12 hours/day, 7 days/week, for 24 weeks	No effect on body weight; significantly increased motor nerve conduction velocity and mixed nerve conduction velocities after 4 weeks of exposure, but not after 24 weeks; significantly decreased distal motor latency after 4 weeks of exposure, but not after 24 weeks.	Takeuchi et al., 1983
Rats/NR	NR	NR	0 or 1125 ppm (0 or 3318 mg/m³) continuously for 5 months	No neuropathy, defined in terms of paralysis, was observed. No other toxicological endpoints were evaluated.	Saida et al., 1976
Rats/NR	NR	25	0 or 235 ppm (0 or 693 mg/m³), 7 hours/day, 5 days/week, for 7 weeks	No significant difference from controls in growth, hematological or pathological examination.	LaBelle and Brieger, 1955
Rats/Sherman	M/F	15/sex/ exposure level	0, 125, 250, 500 or 1000 ppm (0, 369, 737, 1475 or 2949 mg/m³), for 30 days (hours/day and days/week, NR)	No significant histopathological changes in lung, liver or kidney.	Mellon Institute, 1950
Guinea pigs/NR	NR	15	0 or 235 ppm (0 or 693 mg/m³), 7 hours/day, 5 days/week, for 7 weeks	No significant difference from controls in growth, hematological or pathological examination.	LaBelle and Brieger, 1955
Guinea pigs/ mixed strains	M	10/dose level	0, 125, 250, 500 or 1000 ppm (0, 369, 737, 1475 or 2949 mg/m³), for 30 days (hours/day and days/week, NR)	No statistically significant deviation from controls in body, liver or kidney weights.	Mellon Institute, 1950

*Purity of compound was not reported

NR = Not reported

LaBelle and Brieger (1955) observed no effects of exposure to 0 or 235 ppm (0 or 693 mg/m³) of methyl ethyl ketone, 7 hours/day, 5 days/week, for 12 weeks, on growth, hematological or pathological parameters of a group of 25 rats. Although the growth of the rats in the exposed group was less than the controls, no statistical analysis was provided. Information on the specific organs evaluated pathologically was not provided. Guinea pigs presumably exposed to the same level exhibited no adverse effects on growth, hematology or histopathology from the treatment. Similarly, exposure to 0, 125, 250, 500 or 1000 ppm of the compound for 30 days had no effect on rats and guinea pigs (Mellon Institute, 1950); however, details of exposure were not provided.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic oral toxicity of methyl ethyl ketone to humans or experimental animals were not located in the available literature.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of methyl ethyl ketone to humans or experimental animals were not located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of methyl ethyl ketone following oral administration were not located in the available literature.

3.3.2. Inhalation. Schwetz et al. (1974) exposed groups of 21-47 pregnant Sprague-Dawley rats to methyl ethyl ketone by inhalation at levels of 0, 1000 or 3000 ppm (0, 2949 or 8848 mg/m³) for 7 hours/day on days 6-15 of gestation. There was no maternal toxicity at either exposure level.

Somewhat decreased fetal body measurements (body weight and crown-to-rump length) were seen at the lower but not at the higher exposure level. At the 1000 ppm level, there was a significant increase in the percentage of litters having at least one fetus with a skeletal abnormality; however, there was no significant increase in gross, soft-tissue or specific skeletal anomalies. At the 3000 ppm level, a significant increase in litters having fetuses with gross external anomalies or internal soft-tissue anomalies was seen. Schwetz et al. (1974) concluded that methyl ethyl ketone was fetotoxic and potentially teratogenic, but not maternotoxic to rats exposed at levels of 1000 or 3000 ppm during days 6-15 of gestation.

Deacon et al. (1981) conducted an experiment to clarify the results of the study reported by Schwetz et al. (1974). Groups of 25 pregnant Sprague-Dawley rats were exposed to methyl ethyl ketone by inhalation at levels of 400, 1000 or 3000 ppm (1180, 2949 or 8848 mg/m^3), 7 hours/day on days 6-15 of gestation. A control group of 35 pregnant rats was maintained. No maternal effects of toxicity were noted at the two lower concentrations and only a decrease in body weight gain of the dams was reported at the high exposure level. Five fetuses among all the groups, including controls, had at least one malformation upon examination for external and soft tissue malformation. Details of these malformations are discussed in U.S. EPA (1985a). Deacon et al. (1981) concluded that methyl ethyl ketone was not teratogenic in rats, because of the low incidence and the distribution of the malformations observed in the pups. Fetotoxicity was, however, manifested as an increased incidence of extra ribs and of delayed ossification in the cervical centra at the high exposure level only.

3.4. TOXICANT INTERACTIONS

Combined exposure to 100 ppm of n-hexane and 200 ppm of methyl ethyl ketone for 24 weeks resulted in neurotoxic effects (defined as changes in motor nerve conduction velocity, distal motor latency and mixed nerve conduction velocities) in rats that were not observed when either chemical was tested by itself (Takeuchi et al., 1983). Methyl ethyl ketone has also been shown to potentiate the effect of n-hexane on the alveolar epithelium of rats exposed to the mixture for 8 hours/day for $\leq$89 days (Schnoy et al., 1982). Although lesions were not demonstrable by light microscopy, ultrastructural examination revealed the presence of fatty deposits in Type I and II pneumocyte cells.

Hewitt et al. (1983, 1986) found that methyl ethyl ketone potentiated the hepatotoxic action of chloroform in rats. In the earlier study, a significant positive correlation was shown between the carbon chain length of ketones and the severity of the potentiated chloroform-induced liver damage. In the later study, it was determined that choleotasis resulted from potentiation of chloroform-induced alterations in canalicular membrane permeability.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic effects of exposure to methyl ethyl ketone on humans were not located in the available literature.

4.2. BIOASSAYS

Pertinent data regarding the carcinogenic effects of oral or inhalation exposure to methyl ethyl ketone on experimental animals were not located in the available literature. No tumors were observed on the skin of mice after dermal application of 50 mg of methyl ethyl ketone twice weekly for 1 year (U.S. EPA, 1985a). Methyl ethyl ketone is not scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1987).

4.3. OTHER RELEVANT DATA

Methyl ethyl ketone was negative for reverse mutation when tested in Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537 with or without metabolic activation (Florin et al., 1980; Douglas et al., 1980). Methyl ethyl ketone has been shown, however, to be a strong inducer of aneuploidy in the diploid D61.M strain of Saccharomyces cerevisiae (Zimmermann et al., 1985). When ineffective low levels of methyl ethyl ketone were combined with ineffective low levels of nocodazole, another inducer of aneuploidy in this system, significantly elevated levels of aneuploidy resulted (Mayer and Goin, 1987).

4.4. WEIGHT OF EVIDENCE

Methyl ethyl ketone has not been tested for carcinogenicity by the oral or inhalation routes. No tumors were observed in the only dermal exposure study as seen in Section 4.2. (U.S. EPA, 1985a). IARC has not evaluated the risk to humans associated with oral or inhalation exposure to methyl ethyl

ketone. Because of lack of evidence, methyl ethyl ketone is classified as a U.S. EPA Group D chemical; that is, not classifiable as to human carcinogenicity.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1986a) set a TLV-TWA of 200 ppm (590 mg/m³) and a STEL of 300 ppm (885 mg/m³) for methyl ethyl ketone; the basis for these standards is the minimization of eye and nose irritation, and systemic toxic effects are not expected to develop at this exposure level (ACGIH, 1986b).

The NIOSH (1978) recommendation and OSHA (1985) PEL for methyl ethyl ketone are both 200 ppm (590 mg/m³).

ACGIH (1986b) summarized the occupational standards and their year of establishment in other countries as follows: 200 ppm in West Germany (1974); 150 ppm in Sweden (1974); 100 ppm in East Germany (1973); and 100 ppm in USSR (1966), Yugoslavia (1971) and Hungary (1974).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The lack of subchronic oral toxicity data precludes the derivation of an RfD_{SO} for subchronic exposure to methyl ethyl ketone based on oral data. U.S. EPA (1985a) derived a chronic oral RfD_O of 3 mg/day based on the subchronic rat inhalation study reported by LaBelle and Brieger (1955). Derivation of the RfD will follow in Sections 6.1.2. and 6.2.1. Therefore, it would be appropriate to use the subchronic rat NOAEL of 46 mg/kg/day, adjusted for oral route by multiplying the inhalation NOAEL by an absorption factor of 0.5, as the basis for an RfD_{SO} for methyl ethyl ketone. Applying an uncertainty factor of 100 (10 for both inter- and intraspecies variability) to the rat NOAEL of 235 ppm (693 mg/m³), converted to 46 mg/kg/day, results in an RfD_{SO} of 0.5 mg/kg/day or 32 mg/day. Medium confidence is placed in the RfD_{SO} as discussed in Section 6.2.1.

6.1.2. Inhalation (RfD_{SI}). As reported in Section 3.1.2., several subchronic inhalation studies have been performed with methyl ethyl ketone. Two of these studies were considered not useful for risk assessment: the study by Saida et al. (1976) in which only one toxicological endpoint was evaluated and the study by Mellon Institute (1950) in which complete exposure data were not available and a short duration of exposure (30 days) was used.

A NOAEL of 235 ppm (693 mg/m³) for methyl ethyl ketone in rats can be identified from the LaBelle and Brieger (1955) study. For identifying the toxic threshold for methyl ethyl ketone, the studies by Cavender et al. (1983) and Takeuchi et al. (1983) are useful, as both also define a NOAEL. NOAELs of 2500 ppm (7373 mg/m³) for increased SGPT activity in female rats (Cavender et al., 1983) and 200 ppm (590 mg/m³) for temporary slight neurological effects of unknown biological significance in rats (Takeuchi et

al., 1983) were identified from these studies. According to the analysis provided by the U.S. EPA (1985a,b), the NOAEL from the LaBelle and Brieger (1955) study provides the lowest and most protective dose and is therefore the study of choice for deriving the RfD_0. Additionally, methyl ethyl ketone was also tested for teratogenicity (Schwetz et al., 1974; Deacon et al., 1981) and the observed LOAEL, estimated to be 130.5 mg/kg/day for fetotoxicity from the Schwetz et al. (1974) study (U.S. EPA, 1985b), was higher than the NOAEL estimated from the data of LaBelle and Brieger (1955). The NOAEL of 235 ppm (693 mg/m³) from the rat subchronic inhalation study (LaBelle and Brieger, 1955) converts to 92 mg/kg/day by expanding to continuous exposure and using 0.223 m³/day as a reference inhalation rate for rats and a reference body weight for rats of 0.35 kg as follows: 693 mg/m³ x (7/24 hours/day) x (5/7 days/week) x 0.223 m³/day/0.35 kg = 92 mg/kg/day. Applying an uncertainty factor of 100 (10 for both intra- and interspecies extrapolation), results in an RfD_{SI} of 0.9 mg/kg/day or 64 mg/day for a 70 kg man. Confidence in this RfD_{SI} is medium as discussed in Section 6.2.1.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). U.S. EPA (1985a) derived a chronic RfD of 3 mg/day for methyl ethyl ketone from the rat subchronic inhalation study reported by LaBelle and Brieger (1955). The NOAEL of 235 ppm (693 mg/m³) converts to 46 mg/kg/day by using the methodology presented in Section 6.1.2. and also using an absorption factor of 0.5 to extrapolate from inhalation to oral exposure. Applying an uncertainty factor of 1000 (10 for both intra- and interspecies variability and 10 to extrapolate from subchronic to chronic data), results in the chronic RfD_0 of 0.05 mg/kg/day or 3 mg/day for a 70 kg man. This value is verified and available on IRIS (U.S. EPA, 1985b).

Confidence in the study was rated medium because only 25 rats were exposed to only one dose and the control group was not characterized. The data base was given a medium rating because four other studies support the NOAEL. Therefore, confidence in the RfD was rated medium (U.S. EPA, 1985b).

6.2.2. Inhalation (RfD_I). Using the methodology discussed in Section 6.1.2. and applying an additional uncertainty factor of 10 to expand from subchronic to chronic exposure to the RfD_{SI} of 0.9 mg/kg/day or 64 mg/day results in a chronic RfD_I of 0.09 mg/kg/day or 6 mg/day. This chronic RfD_I was derived for interim purposes only and the issue of the inhalation RfD for methyl ethyl ketone is pending verification by the RfD Workgroup.

A CS of 9.6 was derived by the U.S. EPA (1985a) based on the decreased weight gain effects reported in the LaBelle and Brieger (1955) study at 235 ppm (693 mg/m³). Discussion and details of the derivation are presented in the U.S. EPA (1985a) document. The human MED of 110 mg/day corresponds to an RV_d of 2.4 and the effects of decreased body weight warranted an RV_e of 4, resulting in a CS of 9.6.

6.3. CARCINOGENIC POTENCY (q_1^*)

Methyl ethyl ketone is classified as a U.S. EPA Group D chemical; that is, not classifiable as to human carcinogenicity because of lack of evidence for carcinogenicity.

The lack of carcinogenicity data precludes the derivation of a carcinogenic potency for exposure to methyl ethyl ketone.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1986a. Threshold Limit Values for Chemical Substances in the Workroom Environment adopted by ACGIH. Cincinnati, OH. p. 24.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986b. Methyl Ethyl Ketone. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. p. 395.

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg and E.J. Garalla. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3(4): 264-270.

Deacon, M.M., M.D. Pilny, J.A. John, et al. 1981. Embryotoxicity and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 59(3): 620-622. (Cited in U.S. EPA, 1985a)

Dietz, F.K. and G.J. Traiger. 1979. Potentiation of carbon tetrachloride hepatotoxicity in rats by a metabolite of 2-butanone: 2,3-Butanediol. Toxicology. 14(3): 209-215. (Cited in U.S. EPA, 1985a)

Dietz, F.K., M. Rodriguez-Glaxola, G.J. Traiger, V.J. Stella and K.J. Himmelstein. 1981. Pharmacokinetics of 2-butanol and its metabolites in the rat. J. Pharmacokinet. Biopharm. 9(5): 553-576. (Cited in U.S. EPA, 1985a)

Douglas, G.R., E.R. Nestmann, J.L. Betts, et al. 1980. Mutagenic activity in pulp mill effluents. Water Chlorination: Environ. Impact Health Eff. 3: 865-880. (Cited in U.S. EPA, 1985a)

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 15: 219-232. (Cited in U.S. EPA, 1985a)

Graedel, T.E. 1978. Chemical Compounds in the Atmosphere. Academic Press, NY. p. 187.

Hansch, C. and A.J. Leo. 1985. MedChem Project Issue No. 26. Pomona College, Claremont, CA.

Hewitt, W.R., E.M. Brown and G.L. Plaa. 1983. Relationship between the carbon skeleton length of ketonic solvents and potentiation of chloroform-induced hepatotoxicity in rats. Toxicol. Lett. 16(3-4): 297-304. (CA 98:22111146)

Hewitt, L.A., P. Ayotte and G.L. Plaa. 1986. Modifications in rat hepato-biliary function following treatment with acetone, 2-butanone, 2-hexanone, mirex, or chlordecone and subsequently exposed to chloroform. Toxicol. Appl. Pharmacol. 83(3): 465-473. (Taken from MEDLINE Database File 154 on Dialog, Accession No. 86209163)

LaBelle, C.W. and H. Brieger. 1955. Vapour toxicity of a composite solvent and its principal components. Arch. Ind. Health. 12: 623-627. (Cited in U.S. EPA, 1985a)

Lande, S.S., P.R. Durkin, D.H. Christopher, P.H. Howard and J. Saxena. 1976. Investigation of selected potential environmental contaminants: Ketonic solvents. Prepared under Contract No. 68-01-3100. Office of Toxic Substances, U.S. EPA, Washington, DC. EPA 560/2-76-003.

Mayer, V.W. and C.J. Goin. 1985. Effects of chemical combinations on the induction of aneuploidy in Saccharomyces cerevisiae. Mutat. Res. 187(1): 21-30. (Taken from MEDLINE Database File 154 on Dialog, Accession No. 87090136)

Mellon Institute. 1950. Methyl Ethyl Ketone, Report 14-33, unpublished, Union Carbide Corporation. (Cited in U.S. EPA, 1985a)

Miyasaka, M., M. Kumai, A. Koizumi, et al. 1982. Biological monitoring of occupational exposure to methyl ethyl ketone by means of urinalysis for methyl ethyl ketone itself. Int. Arch. Occup. Environ. Health. 50(2): 131-137. (Cited in U.S. EPA, 1985a)

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Ketones. U.S. DHEW, PHS, CDC. Cincinnati, OH. Publ. No. 78-173. (Cited in U.S. EPA, 1985a)

NLM (National Library of Medicine). 1987. Hazardous Substance Data Base. Report No. 99. On-Line.

NTP (National Toxicology Program). 1987. Management status report produced from NTP Chemtrack System. Data received up to 01/09/87. NTP, Research Triangle Park, NC.

OSHA (Occupational Safety and Health Administration). 1985. OSHA Occupational Standards, Permissible Exposure Limits. 29 CFR 1910.1000.

Papa, A.J. and P.D. Sherman, Jr. 1981. Ketones. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 13, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 894-941. (Cited in U.S. EPA, 1985a)

Perbellini, L., F. Brugnone, P. Mozzo, V. Cocheo and D. Caretta. 1984. Methyl ethyl ketone exposure in industrial workers: Uptake and kinetics. Int. Arch. Occup. Environ. Health. 54(1): 73-81. (Cited in U.S. EPA, 1985a)

Saida, K., J.R. Mendell and H.S. Weiss. 1976. Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J. Neuropathol. Exp. Neurol. 35: 207-225.

Schnoy, N., R. Schmidt, A. Altendirch and A.M. Wagner. 1982. Ultrastructural alteration of the alveolar epithelium after exposure to organic solvents. Respiration. 43: 221-231. (Cited in U.S. EPA, 1985a)

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28(3): 452-464.

Takeuchi, Y., Y. Ono, N. Hisanaga, et al. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br. J. Ind. Med. 40(2): 199-203.

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1983. Reportable Quantity Document for 2-Butanone (Methyl ethyl ketone). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1984. Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Methyl Ethyl Ketone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985b. Integrated Risk Information Systems (IRIS). Reference dose (RfD) for oral exposure for methyl ethyl ketone. On-line (Verification date 7/8/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemistry, 2nd ed. Van Nostrand Reinhold Co., NY. p. 850-852.

Zimmermann, F.K., V.W. Mayer, I. Scheel and M.A. Resnick. 1985. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat. Res. 149(3): 339-351. (Taken from MEDLINE Database File 154 on Dialog, Accession No. 85188025)

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APPENDIX

Summary Table for Methyl Ethyl Ketone

	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	rat	235 ppm (693 mg/m³), 7 hours/day, 5 days/ week for 12 weeks (92 mg/kg/day)	NOAEL	64 mg/day	LaBelle and Brieger, 1955
RfD_I (formerly AIC)	rat	235 ppm (693 mg/m³), 7 hours/day, 5 days/ week for 12 weeks (92 mg/kg/day)	NOAEL	6 mg/day	LaBelle and Brieger, 1955
Maximum CS	rat	235 ppm (693 mg/m³), 7 hours/day, 5 days/ week for 12 weeks (92 mg/kg/day) (RV_d = 2.4)	decreased body weight gain (RV_e = 4)	CS = 9.6	LaBelle and Brieger, 1955; U.S. EPA, 1985a
Oral					
RfD_{SO}	rat	235 ppm (693 mg/m³), 7 hours/day, 5 days/ week for 12 weeks (46 mg/kg/day)	NOAEL	32 mg/day	LaBelle and Brieger, 1955
RfD_O	rat	235 ppm (693 mg/m³), 7 hours/day, 5 days/ week for 12 weeks (46 mg/kg/day)	NOAEL	3 mg/day	LaBelle and Brieger, 1955; U.S. EPA, 1985a,b